Exhibit 201

Penn Medicine

Department of Medicine

University *of* Pennsylvania School *of* Medicine

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I have been asked to formally review Dr. Edward H. Kaplan's Expert Report and I am directly addressing his assertions and recommendations for an enhanced screening/monitoring protocol for asymptomatic individuals who took valsartan containing drugs (VCDs) during the time in which the NMDA/NDEA impurity existed. I will specifically address the principles of cancer screening and Dr. Kaplan's screening recommendations as they pertain to the sites of cancers for which he recommends enhanced monitoring.

This report is offered pursuant to Rule 26 of the Federal Rules of Civil Procedure. Each of the opinions offered in this report are given to a reasonable degree of medical probability and/or certainty. I have used the same methods of literature search and research review that I use in my own professional practice as a treating medical oncologist and active cancer researcher. I utilized pubmed.org to conduct a complete literature search of clinical trials and reviews available internationally. The facts and data presented are based on the same principles that I use in my medical oncology practice. I have used my education, training and experience in cancer treatment and screening to analyze these data, guidelines, and to research and to prepare this report.

Please find attached "Exhibit A," which is a list of the documents pertinent to this case that I have read and reviewed.

1. Expert Background and Qualifications

I am a medical oncologist, currently licensed to practice medicine in the states of Pennsylvania and New Jersey. I am fellowship trained and boarded in Medical Oncology as well as Geriatric Medicine and I am boarded in Palliative Medicine. I completed my undergraduate degree at Duke University and my Doctor of Medicine at the University of Maryland School of Medicine. I received Alpha Omega Alpha honors in my junior year of medical school and graduated summa cum laude, Valedictorian of my medical school class. I completed my Internal Medicine internship and residency at the University of Chicago and stayed on to complete two fellowships in Medical Oncology and Geriatric Medicine. I was the second awardee of the ASCO Geriatrics/Oncology Training Program Development Grant through the Hartford Foundation. I also completed the Clinical Research Training Program (certificate) while at University of Chicago. After one year on faculty at University of Chicago, I joined the faculty at University of Pennsylvania School of Medicine in January, 2007.

At the University of Chicago, I served clinical time in Medical Oncology outpatient clinics as well as primary care clinics and dedicated Geriatrics clinics. This is relevant since during my residency, fellowship training, and time on faculty, I was directly caring for patients in a primary care setting and following standard, established screening protocols, including cancer screening

protocols. My geriatric primary care practice was dedicated to care of patients 65 and older. The educational focus was on managing primary care for patients on a spectrum from healthy aging to frailty, all while balancing the comorbidities, functional status and the personal wishes of the patient. I am familiar with prescribing and managing VCDs in the primary care setting as an important medication for hypertension as well as for treatment after acute coronary syndrome and/or for patients with heart failure and chronic kidney disease. This is a particularly important drug class for patients intolerant of ACE inhibitors due to cough and allergy.

At the University of Pennsylvania, I have practiced clinically for 15 years in the subspecialty of Gastrointestinal Oncology, including esophageal, gastric, pancreatic, hepatobiliary, colorectal, small bowel, neuroendocrine, and anal canal cancers. I am one of the few in our medical oncology practice at the University of Pennsylvania who will assess and treat cancers of unknown primary. After boarding in Palliative Medicine in 2012, I started an embedded Supportive Oncology clinic in the Hematology/Oncology division that is now a dedicated Palliative Care Program.

I serve as the Clinical Director of the Penn Pancreatic Cancer Research Center and in this role, I work to prioritize and manage our Clinical Trial portfolio. We participate in collaborative and institutional trials but have a special interest in innovative investigator initiated trials. I have served in the role of Principal Investigator as well as Sub-Investigator and I am a very active participant and contributor to these early and late phase clinical trials.

I teach extensively including Hematology/Oncology fellows, Internal Medicine residents, and medical students, both in lecture and clerkship forms. I am co-lead of the Hematology/Oncology Fellowship Tumor Board which covers all solid tumors and liquid malignancies. I am the Director of the Multidisciplinary Gastrointestinal Tumor Board as well as the medical oncology lead in multidisciplinary colorectal, esophagogastric and neuroendocrine tumor boards. I work closely in an interdisciplinary fashion with Surgical Oncology, Radiation Oncology, Radiology, Pathology, Interventional Gastroenterology, GI Genetics and Interventional Radiology as well as other specialties in the care of gastrointestinal (GI) cancer patients. I ran the Hematology/Oncology outpatient clerkship for the Perelman School of Medicine and serve as Hematology/Oncology core faculty and residency liaison.

I am currently the Lead for the Pancreas Service Line for the Abramson Cancer Center and as such, I am part of the Gastrointestinal Leadership of the Cancer Service Line. I was appointed the formal reviewer for pancreas research for the ECRI-PENN AHRQ Evidence Based Practice Center. I completed the Cooper Leadership Training Program (certificate) at The Wharton School in 2015. I also serve as EPIC lead for the Division of Hematology/Oncology.

I have received multiple awards during my tenure at University of Pennsylvania including the Humanism and Professionalism Award from the Department of Medicine. I was inducted into the Academy of Master Clinicians in 2014 and named the Deenie Greitzer and Daniel G. Haller MD Gastrointestinal Medical Oncology Professor (endowed professorship) in 2015.

Please find a listing of my education, research publications, abstracts, and talks in my Curriculum Vitae, attached as “Exhibit B.”

2. Dr. Kaplan's Identification of Cancers Meriting Enhanced Monitoring.

Dr. Kaplan states, after review of the reports of Dr. Panigrahy, Dr. Madigan, Dr. Etminan and Dr. Lagana, that the following list of malignancies merit enhanced monitoring. He states that in making this recommendation, he assumes the Plaintiffs' experts are correct in terms of the toxicological and epidemiological profile of NDMA and NDEA, as well as the levels, dosages and duration and use of VCD's with the NDMA and NDEA impurities.

1. Liver cancer
2. Esophageal cancer
3. Gastric cancer
4. Pancreas cancer
5. Colorectal/Intestinal cancer
6. Lung cancer
7. Prostate cancer
8. Bladder cancer
9. Hematologic malignancies (Leukemia, Non-Hodgkin's Lymphoma, Multiple Myeloma)

I will briefly review the epidemiology and risk factors for each of these malignancies and will then review current cancer screening guidelines within the construct of the United States Preventive Services Taskforce (USPSTF) which defines our national guidelines. As a correlate, I have also reviewed American Cancer Society (ACS) and American Society of Clinical Oncology (ASCO) recommendations as well as those of other disease specialty societies. Of note, there is no mention of exposure to NDMA or NDEA as a risk factor for this list of cancers or for any cancers in the consensus screening guidelines from any of these screening or disease specialty organizations.

3. Current Known Risk Factors for Malignancies of Interest.

a. *Hepatocellular Carcinoma – HCC (Liver Cancer)* – Liver cancer has the highest global incidence of any gastrointestinal cancer due to the prevalence of Hepatitis B and C viruses.[1] HCC was the fourth most common cause of cancer death worldwide in 2018. Risk factors are well established and are thought to be based on the presence of cirrhosis from any etiology.[2] The most common etiologies of cirrhosis include the Hepatitis B and C viruses, alcohol related cirrhosis, and nonalcoholic fatty liver disease (NASH).[3] NASH is strongly associated with metabolic syndrome which includes obesity, diabetes, hypertension and high cholesterol/dyslipidemia. Total mortality from hepatocellular carcinoma is increasing in the United States due to cirrhosis from alcohol and likely cirrhosis from NASH. Hepatology Society Guidelines recommend screening for Hepatocellular Carcinoma in patients with an established diagnosis of cirrhosis and/or the high-risk virus Hepatitis B using annual abdominal ultrasound and serum alpha-fetoprotein blood test (AFP)[4] However, there is limited randomized

[1] Bray, F. et al: Global Cancer Statistics, 2018: GLOBOCAN Estimates of Incidence and Mortality For 36 cancers in 185 countries. CA Cancer J Clin 68:394-424, 2018.
[2] Gomaa AI, Kahn SA, Toledano MD, et al: Hepatocellular Carcinoma: Epidemiology, Risk factors and Pathogenesis. World J Gastroenterology 14:4300-8, 2008.
[3] Liu X, Ju W, Huo C, et al: Overweight and Obesity as Independent Factors for Increased Risk of Hepatocellular Cancer-Related Mortality: A Meta-Analysis: J Am Coll Nutr: 1-7, 2020.
[4] Davila JA, Morgan RO, Richardson PA, et al: Use of Surveillance for Hepatocellular Carcinoma among Patients with Cirrhosis in the United States. Hepatology 52: 132-41, 2010.

clinical trial data or any evidence to date to show that any HCC surveillance programs reduce disease-related mortality.[5] Of note, abdominal ultrasound and AFP testing for known cirrhotic patients or patients with Hepatitis B are not included in the formal USPSTF cancer screening guidelines.[6] Curiously, in his list of recommended testing, Dr. Kaplan does not recommend any potential studies directed at early detection of Hepatocellular Carcinoma, even though he lists liver cancer as a cancer of concern. Hepatocellular Carcinoma comes up frequently in the Plaintiffs' expert opinions as a likely site of developing malignancy.

b. *Esophageal Cancer* – Esophageal cancers typically develop in the setting of a metaplastic epithelium, which is a condition commonly known as Barrett's Esophagus (BE).[7] In Barrett's Esophagus, the normal squamous lining of the lower esophagus is replaced with a simple columnar epithelium with goblet cells, similar to the cells present in the small and large bowel. Barrett's Esophagus is a premalignant condition caused by chronic acid exposure. Sixty percent of esophageal adenocarcinomas arise in a background of Barrett's Esophagus. Risk factors for BE include male sex, advanced age, gastroesophageal reflux disease (GERD), smoking, diabetes and obesity. BE is most commonly associated with a Western diet and metabolic syndrome. The incidence of BE in patients who are symptomatic with GERD at endoscopy is 10-20%, and it is estimated that 5.6% of adults in the U.S. have underlying Barrett's Esophagus.[8] In a Danish population study, the relative risk of developing esophageal adenocarcinoma in the setting of BE is 11.3 relative to general risk.[9] The annual risk of developing esophageal/GE junction adenocarcinoma in the setting of BE is 1-3%, depending on the reference. Of note there is no consensus guideline on recommended number and timing of screening endoscopies, even in this setting of BE, an established cancer precursor.[10] There is no proof that regular endoscopies detect curable neoplasia and the logistics of performing a randomized trial to prove that screening and surveillance prevent deaths from esophageal cancer are daunting.[11] Screening for and surveillance of Barrett's Esophagus is a controversial topic among Gastroenterology societies and no guidelines exist in USPSTF recommendations for serial endoscopy. The risk management and treatment of Barrett's Esophagus is anti-reflux medications. There is a profound increase in esophageal adenocarcinoma in the past 40 years in Western countries that is not explained by the presence of GERD or incidence of Barrett's Esophagus.

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[5] Harris et al. Hepatocellular carcinoma surveillance: An evidence-based approach. World Journal of Gastroenterology April 7; 25(13): 1550-1559. 2019.

[6] U.S. Preventative Services Task Force: Published Recommendations per website – accessed January 2, 2022.

[7] Shaheen N, Ransohoff DF: Gastroesophageal Reflux, Barrett Esophagus, and Esophageal Cancer: Scientific Review. JAMA 287: 1972-81, 2002.

[8] Spechler SJ, Souza RF. Barrett's Esophagus: N Engl J Med 371: 836-45, 2014.

[9] Hvid-Jensen F, Pedersen L, Drewes AM, et al: Incidence of Adenocarcinoma among Patients with Barrett's Esophagus. N Engl J Med 365: 1375-83, 2011.

[10] Schuchert MJ, Luketich JD: Management of Barrett's Esophagus. Oncology (Williston Park) 21:1382-9, 1392; discussion 1392 1394, 1396.

[11] Spechler SJ. Barrett esophagus and risk of esophageal cancer: a clinical review. JAMA 2013; 310: 627-36.

c. *Gastric Cancer* – Gastric cancer is typically adenocarcinoma and it is one of the quintessential cancers of aging.[12] Risk factors also include being male and /or Black. The incidence in the U.S. has DECREASED markedly over the past 100 years though gastric cancer is still a major concern globally. Environmental factors that increase the risk of developing gastric cancer include high salt diet, high fat diet, low Vitamin A and C intake, large consumption of smoked and cured foods, lack of refrigeration and poor access to clean drinking water.[13] Occupational exposures, which include rubber, asbestos and coal, also increase risk as does cigarette smoking, H. Pylori[14] and radiation.[15] Genetic risk factors include Type A blood (more common in Asia), pernicious anemia, and a family history including known hereditary cancer syndromes. The role of H. Pylori in gastric carcinogenesis is also well defined – H. pylori is a common bacterial infection (30-40% in US).[16] Of note, despite established increased risk of gastric cancer in patients with known H. Pylori, there is no recommendation for screening upper endoscopy per USPTF guidelines.

d. *Pancreatic Ductal Adenocarcinoma (PDAC)* – Pancreas cancer is a very morbid diagnosis – the annual incidence and annual death rate are almost equal. Pancreas cancer is another quintessential cancer of aging, with older age being the greatest known risk factor. Other risk factors include diabetes, chronic pancreatitis, intraductal papillary mucinous neoplasms of the pancreas (IPMNs), obesity, tobacco, sedentary lifestyle and high fat diet.[17] There are no strong environmental factors identified to significantly increase risk, but there is a mild association with chlorinated hydrocarbon solvents, nickel, chromium, organochlorine insecticides and silica.[18] We are learning a lot about the contribution of hereditary cancer syndromes (germline mutations) that may underlie development of pancreatic cancer and this has led to ASCO (American Society of Clinical Oncology) guidelines to recommend genetic testing of all newly diagnosed pancreatic cancers.[19] Of note, Cancer Risk Evaluation Centers follow patients with known pancreas cancer risk syndromes but endoscopic, imaging, or multi cancer early detection tests for surveillance for these patients known to be at increased risk for developing pancreas cancer are not routinely recommended. Clinical trials are underway assessing the benefit and risk of scheduled Endoscopic Ultrasound. The Cancer of the Pancreas Screening Study (CAPS) is an ongoing international multicenter study assessing if screening for pancreatic cancer in high-risk individuals can improve survival and if existing tools can segregate potentially life threatening lesions from low risk lesions. The majority of patients in this study have high risk germline mutations like BRCA. A

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[12] Sehdev A: Gastroesophageal Cancer: Focus on Epidemiology, Classification, and Staging. Discov Med 16:103-11, 2013.

[13] Liu C, Russell RM: Nutrition and Gastric Cancer Risk: an Update. Nutr Rev 66: 237-49, 2008.

[14] Ekstrom AM, Eriksson M, Hannson LE et al: Occupational Exposures and Risk of Gastric Cancer in a Population-based Case-Control Study. Cancer Res 59: 5932-7, 1999.

[15] Dong J, Thrift AP: Alcohol, Smoking, and Risk of Oesophago-gastric Cancer. Best Pract Res Clin Gastroenterol 31: 509-517, 2017.

[16] Fuccio L, Eusebi LH, Zagari RM, et al: Helicobacter pylori eradication treatment reduces but does not abolish risk of gastric cancer. Am J Gastroenterol 104:3100, 2009.

[17] Lowenfels AB, MNguyen LH, Liu PH, Zheng X: Epidemiology and Risk Factors for Pancreatic Cancer: Best Pract Res Clin Gastroenterol 20: 197-209, 2006.

[18] Das K, Early D: Pancreatic Cancer Screening. Curr Treat Options Gastro 15:562-575, 2017.

[19] Lowery MA, Wong W, Jordan EJ, et al: Prospective Evaluation of Germline Alterations in Patients with Exocrine Pancreatic Neoplasms. J Natl Cancer Inst 110: 1067-1074, 2018.

BRCA mutation can occur in either of the BRCA 1 and BRCA 2 genes which are tumor suppressor genes. Mutations in these genes strongly predispose patients to breast, ovarian, prostate and pancreas cancer. Of note, in prior studies of screening in high risk patients, while MRI and Endoscopic Ultrasound identified cysts and solid lesions of the pancreas, none of the pathology at surgery revealed frank malignancy.

e. *Colorectal/Intestinal* – The development of colorectal cancers is associated with many factors including high risk genetic syndromes (for which there are established recommendations for enhanced screening), high fat and high red meat diet, obesity/metabolic syndrome, sedentary lifestyle, inflammatory bowel disease (Crohn's Disease and Ulcerative Colitis), diabetes mellitus, prior radiation, tobacco, alcohol and exposure to asbestos. Colorectal cancers are also cancers of aging which is why there is a defined age at which to start screening. There is a concerning increase in the incidence of colorectal cancer diagnosis at younger ages as identified by the Surveillance, Epidemiology, and End Result (SEER) database and trend of presenting earlier is due to unknown etiology.[20,21,22] The carcinogenesis model of colorectal cancer is very well established from initial formation of a polyp to invasive neoplasia. This requires accumulation of genetic alterations over time to transform to malignancy. This time line has been shown to require many years, decades even, for cancer to develop.[23] There are well established screening tests for asymptomatic patients, the gold standard of which is the colonoscopy. The United States Preventive Screening Task Force guidelines delineate the age and timing for screening of average risk individuals based on extensive effectiveness and safety research. There are enhanced protocols for increased risk patients due to known hereditary cancer syndromes, inflammatory bowel disease or personal history of colorectal cancer.[24] Notably NMDA/NDEA are not identified risk factors for colorectal/intestinal cancers.

f. *Lung* Cancer – While lung cancer remains the most common cause of all cancer deaths, rates are declining in the U.S. due to changes in smoking rates and patterns. Tobacco usage remains the leading risk factor for developing lung cancer, likely contributing to 80% or more of all cases and deaths. Secondhand smoke is also an established risk, albeit much lower.[25] Other risk factors include exposure to radon (2nd leading contributor), asbestos (especially in combination with smoking), radioactive ores and inhaled chemicals including arsenic, beryllium, cadmium, silica, vinyl chloride, nickel, chromium, coal products, mustard gas, chloromethyl ethers and diesel exhaust. Of note, NMDA and NDEA

[20] Wei EK, Giovannuci E, Wu K, et al: Comparison of Risk Factors for Colon and Rectal Cancer. Int J Cancer 108: 433-42, 2004.

[21] Bouvard V, Loomis D, Guyton KZ, et al: Carcinogenicity of Consumption or Red and Processed Meat. Lancet Oncol 16: 1599-600, 2015.

[22] Nguyen LH, Liu PH, Zheng X, et al: Sedentary Behaviors, TV Viewing Time and Risk of Young-Onset Colorectal Cancer. JNCI Cancer Spectr 2, 2018.

[23] Fearon ER, Vogelstein B: A Genetic Model for Colorectal Tumorigenesis. Cell 61: 759-67, 1990.

[24] Burt RW, DiSario JA, Cannon-Albright L: Genetics of Colon Cancer: Impact of Inheritance on Colon Cancer Risk. Annu Rev Med 46: 371-9, 1995.

[25] Sasco aj, Secretan MD, Straif K: Tobacco Smoking and Cancer: a Review of Recent Epidemiological Evidence. Lung Cancer 45 Suppl 2:S3-9, 2004.

are nowhere on the established list of carcinogens or contributors.[26] Despite the number of known possible carcinogens, the vast majority of lung cancer cases are due to tobacco smoking. Because of this association, there was extensive research into screening of smokers, which finally showed a benefit to cancer screening with low dose helical CT scans and this has been formally integrated into USPSTF guidelines.[27] Low dose helical CT was hailed as a tremendous screening breakthrough, meriting publication in the New England Journal of Medicine in 2011.

g. *Prostate Adenocarcinoma* – Prostate cancer is very common worldwide and is actually the hallmark cancer of aging. It is the second most common cancer in men but not the most morbid. The incidence of prostate cancer closely mirrors screening with prostate specific antigen (PSA) and the biopsies that PSA testing prompted, but we have learned that many of these diagnosed cancers are indolent. Prostate cancer is more commonly a cancer men die with and not from.[28,29] While intense cancer screening may detect more prostate cancers, it is not clear that screening and detection changes survival rates. Additionally, the workup for a persistently elevated PSA is trans rectal ultrasound guided biopsy which is invasive and uncomfortable. As such, the USPSTF recommendations have been downgraded and now include stronger recommendations **NOT** to test PSA after age 70. Risk factors also include family history which remains an established reason to screen. Black men are also more at risk and tend to be diagnosed with more aggressive cancers at younger ages. Other risk factors include tobacco, obesity, sedentary lifestyle and some established environmental carcinogens including agent orange, chlordecone and bisphenol.

h. *Bladder* – Bladder cancer is also associated strongly with aging – most newly diagnosed patients are 65 or older. Family history is also an established risk factor. The most modifiable risk factor for development of bladder cancer is tobacco usage. Some associated occupations include metal workers, painters, rubber industry workers, leather workers and many others – the likely environmental compounds they are being exposed to are benzene, paint components, diesel exhaust and polyaromatic hydrocarbons.[30] Other rare risk factors include chronic infection, radiation, and prior chemotherapy. Of note, even in patients with tobacco usage and known exposures, there are **no** recommended screening protocols. There is no data to support routine urinalysis or cystoscopy of high risk patients due to confirmed carcinogenic exposures.

i. *Hematologic malignancies (Leukemia, Non-Hodgkin's Lymphoma, Multiple Myeloma)* – These liquid malignancies are all rare cancers. The bone marrow and these "liquid" cancers have the most rapidly turning over cells in the entire

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[26] Ciabattini M, Rissello E, Lucaroni F, et al: Systematic Review and Meta-Analysis of Recent High-Quality Studies on Exposure to Particulate Matter and Risk of Lung Cancer. Environ Res 196: 110440, 2021.

[27] National Lung Screening Trial Research Aberle DR, Adams AM et al. Reduced Lung-Cancer Mortality with Low-Dose Computed Tomographic Screening. N Engl J Med 365: 395-409, 2011.

[28] Fleshner K, Carrlson SV. The Effect of the USPSTF PSA Screening Recommendation on Prostate Cancer Incidence Patterns in the USA. Nat Rev Urol 14: 26-37.

[29] Force USPST: Screening for Prostate Cancer: U.S. Preventative Services Task Force Recommendation Statement. Ann Intern Med 149: 185-91, 2008.

[30] Zeegers MP, Swaen GM, Kant I. Occupational risk factors for male bladder cancer: results from a population based case cohort study in the Netherlands. Occup Environ Med. 2001; 58 (9); 590.

body and should therefore be the most susceptible to exposure to a confirmed carcinogen/mutagen. There is no known risk for any of these three hematologic malignancies with exposure to NMDA or NDEA.

i. Leukemia: Acute myelogenous leukemia (AML) is the most common leukemia and is strongly associated with aging. The median age at presentation is 65. Environmental exposures that are weakly associated include chemicals, radiation, tobacco and prior alkylating chemotherapies. There are rare genetic associations. There are no screening tests for leukemia.[31]

ii. Lymphoma: While Dr. Kaplan mentions Non-Hodgkin's Lymphoma specifically, I reviewed susceptibility factors for all lymphomas since they are all cancers of the lymphatic system. Lymphomas are also cancers of aging and there are no identifiable risk factors/exposures beyond some note of familial case clusters. There are no known screening tests for any lymphomas.

iii. Multiple Myeloma: Multiple myeloma is an uncommon cancer without known risk factors beyond advanced age, race, and a mild increase in risk with an elevated body mass index. No screening test exist or are recommended.

4. Principles of Cancer Screenings in Asymptomatic Populations:

1. Early identification of cancer
2. Goal of early diagnosis
3. Chance for improved control/cure

There are well established and validated screening protocols for defined cancers set forth by the USPSTF (see USPSTF website). The absolute benefit of these screening tests is **graded** based on a systemic review of available evidence. The founding principle of these screening protocols for primary care is the balancing of possible preventative benefit of tests with the real risk of harm from inappropriate testing. There is no consideration of cost in the USPTF guidelines. Patients often do not understand that tests without reasonable pre-test probability may not confer benefit and can cause actual harm including anxiety, over diagnosis, and complications from invasive cancer workups. There are many dedicated experts in the cancer screening field that convene to assess the strength of the existing data and to create consensus guidelines on the appropriateness of testing for any given cancer in any given population. The only cancers for which formal screening guidelines/recommendations exist are for colorectal cancer, breast cancer, cervical cancer, prostate, and lung cancer. For each of these five cancers, there are strict age criteria prior to testing and the only reasons for enhanced screening are familial cancer syndromes, prior personal history of cancer, and tobacco history.

Of note, there are no recommendations for enhanced screening for any other exposure or known condition besides smoking. There are no USPTF recommendations to actively screen asymptomatic patients for any other cancers. While there are some disease specialty society guidelines with recommendations on specific enhanced testing including endoscopic surveillance for Barrett's Esophagus and Ultrasound/AFP testing for patients with known cirrhosis, there are no nationally/internationally recognized consensus guidelines for screening

[31] Smith A, Howell D, Patmore R, Jack A, Incidence of Haematological Malignancy by Sub-Type: a report from the Haematologic Malignancy Research Network, Br J Cancer, 2011 Nov; 105 (11): 1684-92.

for these conditions. There are notably **NO** USPSTF cancer screening guidelines for Liver, Esophagus, Gastric, Pancreas, Bladder, or Hematologic Malignancies

The USPSTF carefully evaluates and grades the Levels of Evidence as seen in the Tables Below Prior to Making Consensus Cancer Screening Recommendations:

What the Grades Mean and Suggestions for Practice (from USPSTF website)

The USPSTF updated its definitions of the grades it assigns to recommendations and now includes "suggestions for practice" associated with each grade. The USPSTF has also defined levels of certainty regarding net benefit. These definitions apply to USPSTF recommendations voted on after May 2007.

Grade	Definition	Suggestions for Practice
A	The USPSTF recommends the service. There is high certainty that the net benefit is substantial.	Offer or provide this service.
B	The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.	Offer or provide this service.
C	*Note: The following statement is undergoing revision.* Clinicians may provide this service to selected patients depending on individual circumstances. However, for most individuals without signs or symptoms there is likely to be only a small benefit from this service.	Offer or provide this service only if other considerations support the offering or providing the service in an individual patient.
D	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.	Discourage the use of this service.

I Statement	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.	Read the clinical considerations section of USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

Levels of Certainty Regarding Net Benefit

Level of Certainty*	Description
High	The available evidence usually includes consistent results from well-designed, well-conducted studies in representative primary care populations. These studies assess the effects of the preventive service on health outcomes. This conclusion is therefore unlikely to be strongly affected by the results of future studies.
Moderate	The available evidence is sufficient to determine the effects of the preventive service on health outcomes, but confidence in the estimate is constrained by such factors as: • The number, size, or quality of individual studies. • Inconsistency of findings across individual studies. • Limited generalizability of findings to routine primary care practice. • Lack of coherence in the chain of evidence. As more information becomes available, the magnitude or direction of the observed effect could change, and this change may be large enough to alter the conclusion.

Low	The available evidence is insufficient to assess effects on health outcomes. Evidence is insufficient because of: • The limited number or size of studies. • Important flaws in study design or methods. • Inconsistency of findings across individual studies. • Gaps in the chain of evidence • Lack of information on important health outcomes.

(**Reference**: USPSTF Preventive Services Task Force Ratings. Available online at: https://www.uspreventiveservicestaskforce.org/uspstf/us-preventive-services-task-force-ratings).

The goal of the experts meeting prior to publishing guidelines is to establish consensus on benefits of screening tests without respect to cost and, just as importantly, to limit risk of harm from unnecessary or unreliable tests/procedures. While there many available diagnostic tests, when (and if) to order them requires sound medical judgement and an informed, appropriate patient. A decision about a test's appropriateness relies on pretest probability which can also be referred to as disease prevalence. Screening tests recommended by professional medical organizations are based on relatively high incidence of the studied disease AND demonstrated improved survival based on the findings of the test. Of note, most cancers do NOT have routine screening recommendations. As per the USPSTF guidelines above, screening recommendations are based on strength of the evidence and the certainty of the level of benefit. PSA for prostate cancer is among the screening tests recommended and even testing PSA is given faint endorsement with Grade C in ages 55-69, speaking to how complicated and controversial the cancer screening process is. Even though PSA is recommended by USPSTF, the strength of the recommendation is guarded. USPSTF recommends NOT screening (Grade D) for the following specific cancers in asymptomatic adults: Bladder, Pancreas, Ovarian, Thyroid, Testicular cancer.

A & B Recommendations

A listing of Cancer Screening Recommendations with a grade of either A or B

TOPIC	DESCRIPTION	GRADE	DATE
Breast Cancer: Screening: women aged 50 to 74 years	The USPSTF recommends biennial screening mammography for women aged 50 to 74 years. ‡	**B**	January 2016 *
Cervical Cancer: Screening: women aged 21 to 65 years	The USPSTF recommends screening for cervical cancer every 3 years with cervical cytology alone in women aged 21 to 29 years. For women aged 30 to 65 years, the USPSTF recommends screening	**A**	August 2018 *

	every 3 years with cervical cytology alone, every 5 years with high-risk human papillomavirus (hrHPV) testing alone, or every 5 years with hrHPV testing in combination with cytology (cotesting). See the Clinical Considerations section for the relative benefits and harms of alternative screening strategies for women 21 years or older.		
Colorectal Cancer: Screening: adults aged 50 to 75 years	The USPSTF recommends screening for colorectal cancer in all adults aged 50 to 75 years.	**A**	May 2021 *
Lung Cancer: Screening: adults aged 50 to 80 years who have a 20 pack-year smoking history and currently smoke or have quit within the past 15 years	The USPSTF recommends annual screening for lung cancer with low-dose computed tomography (LDCT) in adults aged 50 to 80 years who have a 20 pack-year smoking history and currently smoke or have quit within the past 15 years. Screening should be discontinued once a person has not smoked for 15 years or develops a health problem that substantially limits life expectancy or the ability or willingness to have curative lung surgery.	**B**	March 2021 *

(**Reference**: USPSTF A & B Recommendations. Available online at: https://www.uspreventiveservicestaskforce.org/uspstf/recommendation-topics/uspstf-and-b-recommendations).

C and D Recommendations: Prostate Cancer

Population	Men aged 55 to 69 y	Men 70 y and older
Recommendation	**The decision to be screened for prostate cancer should be an individual one. Grade: C**	**Do not screen for prostate cancer. Grade: D**
Informed Decision Making	Before deciding whether to be screened, men aged 55 to 69 years should have an opportunity to discuss the potential benefits and harms of screening with their clinician and to incorporate their values and preferences in the decision. Screening offers a small potential benefit of reducing the chance of death from prostate cancer in some men. However, many men will experience potential harms of screening, including false-positive results that require additional testing and possible prostate biopsy; overdiagnosis and overtreatment; and treatment complications, such as incontinence and erectile dysfunction. Harms are greater for men 70 years and older. In determining whether this service is appropriate in individual cases, patients and clinicians should consider the balance of benefits and harms on the basis of family history, race/ethnicity, comorbid medical conditions, patient values about the benefits and harms of screening and treatment-specific outcomes, and other health needs. Clinicians should not screen men who do not express a preference for screening and should not routinely screen men 70 years and older.	
Risk Assessment	Older age, African American race, and family history of prostate cancer are the most important risk factors for prostate cancer.	

(**Reference**: USPSTF Prostate Cancer: Screening. Available online at: https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/prostate-cancer-screening).

The only intensified screening protocols per USPSTF are for specific high risk cancers defined by presence of hereditary cancer syndromes/ pathogenic inherited mutations, personal history of malignancy and defined predisposing illnesses (ex. inflammatory bowel disease). The only exposure driven recommendation is for a specified number of pack years of tobacco smoking in a defined age range. There are no USPSTF recommendations for surveillance screening for cirrhosis for hepatocellular carcinoma with the blood test AFP and abdominal ultrasound or Barrett's Esophagus with upper endoscopy. There are also no recommendations for patients with exposure to the known carcinogen asbestos with Low Dose Helical CT for lung cancer detection. The disease societies debate best management and there remains great controversy based on available data. The goal of intensive screening is the hope for early detection at a stage where the malignancy can be intervened upon. There exists real potential risk of HARM in screening, namely patient anxiety, unnecessary invasive tests due to false[32] positives, risk of false negative testing, overdiagnosis and overtreatment, and the tremendous risk of harm created by unnecessary procedures.[33,34] There are also quality control and operator-dependent issues with imaging and invasive procedures such as radiology interpretation, colonoscopy and trans rectal ultrasound.[35] All of the screening test outcomes have potential risk and negative consequences that need to be considered when evaluating whether cancer screening is recommended for any given patient.

Patient Anxiety/Psychologic Distress is an under examined issue with cancer screening[36] and there is minimal research quantify the incidence and severity beyond survey studies. The majority of this data is in the general screening population of patients deemed to have average risk of cancer. The bulk of anxiety is associated with more invasive procedures such as screening colonoscopy. It is unclear what the screening anxiety in this VCD population would be as Dr. Kaplan's recommendation is to assess them as though they are at higher risk than even a patient with a hereditary cancer syndrome or known primary cancer. Patients in established higher risk categories with validated enhanced screening protocols are known to have more psychological distress associated with screening, even if ultimately found to be at average risk. False positives also generate a lot of anxiety at time of the positive test result and with subsequent screening tests. There is limited evidence on methods to reduce the stress associated with false-positive screening findings and workups.

False positive results from cancer screening tests are actually quite common and lead to patient anxiety and distress. Up to 50% of women may receive false positive for screening mammography leading to ultrasound and potential biopsy. 10-12% of men have false positive from PSA testing. PSA testing can also have normal results when a man does in fact have cancer (**False negative result**) which is also potentially detrimental. Almost one quarter of

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[32] Smith, RA, Andrews K, Brooks D et al. Cancer screening in the United States 2019: A review of current American Cancer Society guidelines and current issues in cancer screening. CA Cancer J Clin 69(3): 184-210. May 2019.

[33] Rebbeck TR. Precision Prevention and Early Detection of Cancer: Fundamental Principles. Cancer Discovery 9:803-811, 2018.

[34] Smith, RA et al. Cancer Screening in the United States, 2018: A review of Current American Cancer Society Guidelines and Issues in Cancer Screening. CA Cancer J Clin 68:297-316, 2018.

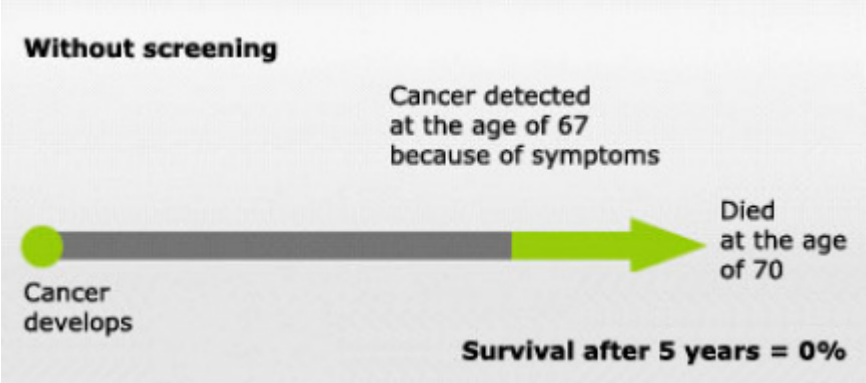
[35] Brawley O, Byers T, Chen A, et al. New American Cancer Society process for creating trustworthy cancer screening guidelines. *JAMA.* 2011; 306:2495-2499.

36 Chad-Friedman et al. Psychological distress associated with cancer screening: A systematic review. *Cancer.* 123(20): 3882-3894, October 15, 2017.

patients who have colonoscopy after a false positive fecal occult blood test will have a negative screening confirmatory colonoscopy.[37]

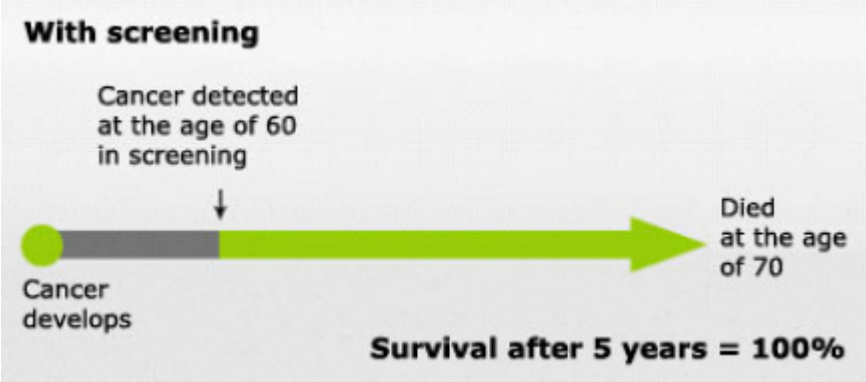
Overdiagnosis is another complication whereby a positive result is found that likely does not change the patient's outcome or survival. Better said, overdiagnosis is a cancer diagnosis detected due cancer screening that would never have been diagnosed in the patient's lifetime in the absence of screening.[38] This cancer diagnosis provides an unfavorable balance between benefit and harm because the detected cancer would not have caused symptoms or led to premature death but these patients likely will have unnecessary procedures, surgeries and toxic systemic therapies, a phenomenon called **Overtreatment**. The cancers most likely to be overdiagnosed through screening are prostate, thyroid, breast and lung, two of which (prostate, lung) are on Dr. Kaplan's list of cancers for enhanced monitoring. The paradoxical problem that is reflected in the screening controversy is that screening is most likely to find the slowest growing or indolent/dormant cancers that are the least likely to harm patients. Screening is less likely to find the aggressive, rapidly progressive cancers that cause the greatest mortality and morbidity.

Thus, screening detects and treats non-threatening cancers at an earlier age, and can give the appearance of a longer survival rate, yet the absolute survival rate of screened and unscreened patients is equivalent and screening does not prolong total lifespan. The following two graphs illustrate the paradox, with two exemplar sets of patients, screened and unscreened, dying at the same age but with different medical experiences in the years preceding death—and the screened group ostensibly enjoying a "longer" survival rate through invasive earlier treatment but no change in the absolute survival rate.



[37] Taksler GB, Keating NL, Rothberg MB. Implications of false-positive results for future cancer screenings. [published online April 23, 2018]. *Cancer*. doi: 10.1002/cncr.31271

[38] Carter, SM, What is Overdiagnosis and Why Should We take it Seriously in Cancer Screening. Public Health Res Pract 2017 Jul 26; 27(3):2731722.



(**Reference** = National Cancer Institute)[39]

Procedure Risk is a very real concern with endoscopy, biopsy (especially trans rectal prostate biopsy), and potentially unnecessary radiation exposure from imaging. Prostate cancer is a great example where overtesting may confer risk as detection of an elevated PSA can lead to increased biopsies and toxic therapies unnecessarily. Cancer screening may detect prostate cancers that would never have been clinically evident yet these cancers are hard to ignore once they are diagnosed and the treatments can lead to urinary, bowel, and sexual dysfunction – some of which may be significant and permanent. PSA testing is very susceptible to false positives leading to anxiety and invasive testing. False positives can also cause sustained unfounded anxiety about an individual's prostate cancer risk. The very act of prostate cancer screening is so fraught that it is recommended to get informed consent in the clinic and to discuss all possible outcomes before even ordering a PSA blood test.

While Low Dose Helical Computed Tomography (LDCT) is recommended for smokers of certain age and pack year history, the clear limitation is that LDCT will not detect all lung cancers early and not all lung cancer patients will have their tumors detected by LDCT. A false positive will necessitate additional testing and possible biopsy. It is estimated that 1 in 1000 patients with false positive on LDCT will experience a major complication from a diagnostic work up. Death within 60 days of a biopsy is rare but reported. The other risk with current smokers is that some will not engage in smoking cessation as they see screening as an alternative.[40]

[39] National Cancer Institute. Crunching Numbers: What Cancer Screening Statistics Really Tell Us. Available online: https://www.cancer.gov/about-cancer/screening/research/what-screening-statistics-mean.

[40] Andrews JC, Schunemann HJ, Oxman AD, et al. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. *J Clin Epidemiol*. 2013; 66: 726-735.

The National Cancers Institute (NCI) defines Effective Screening Tests by the following parameters:[41]

Find Cancer Early

Reduce the chance that someone who is screened regularly will die from the cancer

Have more potential benefits than harms (bleeding, physical damage, inaccurate test results, overdiagnosis)

Cancer screening researchers however hold screening tests to a higher standard. They use statistical methods to assess how reliable a test is and whether or not a patient actually benefits from starting treatment earlier upon screening identification of a cancer. These cancer screening experts also try to identify which populations benefit from early diagnosis and treatment, and how the benefits compare to the risks of cancer screening.

It is important to note that there are NO recommendations for enhanced screening protocols per USPSTF, American Cancer Society, or the American Society for Clinical Oncology for patients with <u>any</u> exposure besides tobacco. NDMA and NDEA are not identified as a risk factor or a carcinogen by any cancer organization or screening guidelines taskforces. The only recognized potential carcinogen requiring additional screening is tobacco for patients with a 20-year pack year history within a defined age range. There are <u>no</u> modifications of the guidelines for any other exposures including the universally accepted carcinogen asbestos. There are also no USPSTF protocols for patients with diagnoses <u>known</u> to substantially increase their risk of developing cancer such as Barrett's Esophagus and cirrhosis. And there is no established benefit to surveillance programs for patients at known increased risk of developing pancreatic cancers because of hereditary cancer syndromes like the BRCA mutation or Lynch Syndrome. Given the lack of definitive evidence that there even exists an increased cancer risk with the NDMA/NDEA contamination in VCDs, an enhanced screening protocol would almost certainly confer more risk than benefit. Additionally, patients taking VCDs are typically older and so would likely be already receiving the recommended cancer screening tests.

In clinical practice in the real world, screening is very individualized and ultimately the decision about which tests to order is made between the patient and their Physician/Provider. The guidelines are just that – recommendations based on available data for an asymptomatic population. Even with a healthy, motivated patient and evidence-based guidelines, the risks and benefits of each test are discussed with the patient so they can make an informed decision. The word Doctor is derived from the Latin "docere" which means "To Teach." A physician's role in the sacred clinic space is to <u>teach</u> the patient about the potential benefits, limitations and harms of screening. Cancer screening is an inherently

[41] National Cancer Institute. Cancer Screening. Available online at: https://www.cancer.gov/about-cancer/screening.

imperfect intervention. The individual assessment and decision making prior to the ordering of each recommended test is almost to the standard of informed consent. The conversation can be quite in depth and time consuming. It is a very intense experience explaining the potential risks and benefits of a test to a patient who is scared about their cancer risk and thinks they wants every screening study available without knowing the tests' limitations of accurate detection. Patients are understandably incredibly fearful of a cancer diagnosis. These conversations currently are particularly difficult given the allotted length of most office visits (15-60 minutes depending on indication for appointment) and new communication barriers with Covid-19.

Comorbidities (including frailty) are serious concerns - for example, if a patient's life expectancy is 5 years or fewer, there is less impetus to put the patient through screening tests designed to find cancers at early stages since the detection might never be clinically relevant in their lifetime. That said, in my experience, elderly patients and patients with significant comorbidities want to live as long and as well as the general population so a list of recommended "enhanced" medical monitoring for an undefined exposure risk would likely cause a lot of anxiety and potential for harm. These older patients with many health conditions (similar to the VCD prescribed population) also have increased risk of complications from recommended tests and screening procedures – an increase in frequency of invasive studies would almost certainly increase their risk of harm.

Analysis of Dr. Kaplan's Proposal for "Routine Screening" for Asymptomatic Individuals Exposed to VCDs.

1. Annual History/Physical and Laboratory Studies
    A. History taking as described is standard in a yearly Primary care visit.
    B. Physical examination as described is standard in a yearly Primary care visit.
    C. Yearly laboratory studies interestingly are not mandated in screening protocols but in general practice may include the following:
        i. Complete blood count (CBC)
        ii. Kidney panel (basic metabolic panel) and in some circumstances, complete metabolic panel (liver and kidney panel), particularly if the patient is taking a statin drug class.
        iii. While thyroid function tests are often performed, they are not routinely recommended and I cannot find any data to support testing in the context of cancer screening. In fact, most of the literature actively discourages routine screening. There are also no clinical trials evaluating effectiveness of screening for hypothyroidism.
        iv. It is unclear what Dr. Kaplan means by "labs for general signs of inflammation or imbalances." I do not know why he recommends these laboratories and what action he would recommend for an abnormal result(s). Possibly, Dr. Kaplan means ESR (Erythrocyte sedimentation rate)and CRP (C-reactive protein).[42] These serum proteins are acute phase reactants that accompany inflammation – CRP was initially described in patients with pneumonia. There is little utility for ordering

[42] Gabay C, Kushner I. Acute phase proteins and other systemic responses to inflammation. N Engl J Med 1999, 340(6): 448.

these non-specific measures of inflammation because they are not particular to any disease process nor are they relevant cancer screening tools. Sometimes ESR and CRP are even discordant in the same patient's laboratory results. An individual has a high risk of these tests being elevated due to many common conditions. Mild elevations of ESR and CRP can be associated with advancing age, female sex, anemia, kidney disease, atherosclerosis, obstructive sleep apnea, hypertension, insulin resistance, and obesity. Poor technique in drawing the blood or processing the laboratory can also increase the levels. Moderate to high elevations can be found in systemic and localized inflammatory diseases (rheumatoid arthritis, lupus, polymyalgia rheumatic, vasculitis), cardiovascular disease, bacterial infections, viral infections, tissue injury, ischemia, trauma and malignancy. The finding of an elevated ESR and/or CRP has a high chance of raising anxiety and prompting testing without any meaningful indication. I have never encountered or heard of using these laboratories as a cancer screening strategy - likely because there are ambiguous and potentially dangerous implications for their use in this setting. In this construct of enhanced medical monitoring, an elevated ESR or CRP may prompt an unnecessary work up for cancer and cause great patient anxiety.

v. Prostate Specific Antigen (PSA) – Per USPSTF, there are very defined criteria for drawing PSA based on family history, age and race. Testing within these parameters has been extensively studied and validated. It must also be noted that PSA is not specifically a test for cancer – there are lots of conditions that can increase PSA including benign prostatic hypertrophy, older age, prostatitis, ejaculation, riding a bicycle and certain medications. Some prescription medications and herbal/alternative medications can actually spuriously lower a PSA level, even if a man has prostate cancer.
    1. A large study in the U.S. found that while annual testing detected more prostate cancers in men that were screened, this PSA screening did not lower the death rate from prostate cancer. A European study showed lower risk of death from prostate cancer with PSA done every 4 years – but 781 men needed to be screened and 27 cancers detected to prevent one death from prostate cancer.[43] Neither of these studies showed PSA screening helped men live longer overall (i.e. lowering the overall death rate). Thus PSA screening confers only a small potential benefit in reducing prostate cancer mortality.
    2. Prostate biopsy is the gold standard test to determine the presence of cancer - this test has very well defined complications, including pain, rectal bleeding, bleeding in urine and sperm, infection and urinary obstruction. Twenty-five percent of patients experienced lower urinary tract symptoms after the procedure, including urinary retention and temporary erectile dysfunction, with full return function usually by 6 months. There is a notable increased incidence of infectious complications after trans rectal ultrasound guided biopsy in patients with medical comorbidities and older age.

[43] American Cancer Society. What's New in Prostate Cancer Research? Available online: www.cancer.org/cancer/prostate-cancer/about/new-research.html.

3. Studies have failed to show support for drawing yearly PSA based on exposure to nitrosamines or any other potential toxins. There is a risk-adjusted approach to testing including age of onset and frequency based on age, race, and family history but even here with unclear benefit from screening. Early and frequent testing of men with hereditary cancer syndromes like BRCA1/2 that are known to predispose them to developing prostate cancer has not definitively shown benefit.

vi. Urinalysis(UA) - Urinalysis is not mandated for screening in the clinic or for any specified malignancy. There is no established benefit or recommendation for yearly UA to screen for bladder or kidney cancer. Studies of screening urine tests, even in workers known to be occupationally exposed to confirmed carcinogens, have been mixed/inconclusive and there are no randomized controlled trials. The top recommendation in kidney/bladder cancer screening/prevention studies is for tobacco-cessation programs.

2. <u>Specialized Testing: Annual recommendations</u>

A. Annual – or more often – is the recommended frequency of these tests by Dr. Kaplan. Annually is a potentially dangerous testing interval, and Dr. Kaplan's suggestion that testing may be required even "more often" than annually is particularly alarming. It is unclear why Dr. Kaplan recommends that any of the invasive tests should be performed more often given the real risk of complications. It is also troubling that Dr. Kaplan recommends a novel test that is under study "annually or more often." His recommendation for annual or more frequent use of an unapproved test is risky to the point of being potentially dangerous.

B. Galleri (Grail) = Multi-Cancer Early Detection test or similar liquid biopsy testing

i. These tests are not FDA approved. Galleri does have IDE (Investigative Device Exemption) for research purposes.

ii. Galleri is not available commercially outside of New York state.

iii. Studies to date are feasibility studies only and do not reflect performance in actual screening populations.

iv. There are no randomized controlled trials in any setting for the Multi-Cancer Early Detection (MCED) tests.

v. The clinical utility of MCEDs, especially in screening, including average and high risk populations, has not been established.

vi. At the 2021 American Society of Clinical Oncology Annual Meeting, a poster was presented by primary investigator Tomasz Beer, MD which represented the most extensive data set available to date.

vii. CCGA study (Circulating Cell-free Genome Atlas) is the initial study with the most mature data. Investigators analyzed blood and tissue samples from patients at 142 sites in North America with and without a cancer diagnosis. The test demonstrated promise for improved detection rates for later stage tumors. 39% for Stage I, 69% Stage II, 83% Stage III.[44] These earlier stages of cancer are similar to what screening guidelines in practice currently are designed to detect.

[44] Liu MD, Oxnard GR CCGA Consortium. Sensitive and specific multi-cancer detection and localization using methylation signatures in cell-free DNA. Ann Oncolo. 2020, 31 (6): 745-759.

viii. At the University of Pennsylvania, we have a CREP (Cancer Risk Evaluation Program) and have **not** adopted use of MCEDs in patients at known high risk of developing specific malignancies based on paucity of evidence.

ix. PATHFINDER is an ongoing intervention study to determine how MCED tests can be integrated in clinical practice. PATHFINDER hopes to enroll 6200 patients in a prospective, longitudinal, interventional multi-center study. If participants have a cancer signal detected, they will undergo diagnostic evaluation per guiding physician discretion. Those with "signal not detected" will continue guideline-recommended screening. The primary objective will be to assess the number and types of subsequent diagnostic tests needed for diagnostic resolution.[45] Study enrollment has been delayed by Covid pandemic.

x. Examples of potential real world scenarios from results of screening MCEDs:

1. If pancreas cancer cells are detected but no obvious cancer found on biochemical, radiographic and endoscopic testing, what would the plan be? Frequent laboratories, imaging and endoscopic ultrasound would be the likely recourse without guarantee of finding an actual mass, particularly if very early in the course or if the cancer is very indolent. Of note, there can be a significant latency period (years) before a cancer becomes measurable and there are even documented incidences of spontaneous regression of tumors. The only curative modality for pancreas adenocarcinoma is surgery and the surgeries (complete pancreatectomy, Whipple, distal pancreatectomy/splenectomy) are very morbid. I cannot imagine any surgeon being willing to perform surgery for a radiographically occult tumor and yet the only way to cure/prevent pancreas cancer is surgery. Enhanced imaging/endoscopy screening protocols have proven unreliable, even at increased frequencies. Biopsy of the pancreas carries a real risk of pancreatitis which is painful and can be life-threatening so random biopsies not an option. I believe this would be a very anxiety provoking scenario for a patient and their primary care physician to navigate.
2. If bladder cancer cells are found but no tumor seen on imaging or cystoscopy, what would the strategy be for identifying and locating the source? Repeat invasive cystoscopies with random biopsies of the bladder wall? Prophylactic cystectomy? Serial MCEDs to assess intensity of cancer signal? Again the only curative modality for bladder cancer is surgery.
3. Esophageal adenocarcinoma cells in a liquid biopsy would prompt repeat upper endoscopies with all associated procedural risks. If no areas of concern seen, the gastroenterologist might need to do random biopsies with associated tattooing to follow sites of interest. Esophagectomy is the most dangerous of all surgeries, riskier than cardiovascular surgeries. Risk of mortality nationally after esophagectomy can be up to 8%.

xi. Liquid Biopsy is an exciting future direction. MCEDs may truly be the "Holy Grail" of cancer detection and surveillance but the technology is not yet clinically validated and supported by sufficient data. Currently,

[45] Nadauld et al. The PATHFINDER Study: Assessment of the Implementation of an Investigational Multi-Cancer Early Detection Test into Clinical Practice. Cancers 2021, 13,2501.

the appropriate populations to screen or if any mortality benefit exists is unknown. Risk profiles have not yet been determined and guidelines on workup and management after positive testing have not yet been formulated.

C. Cologuard (Dr. Kaplan recommends Cologuard or similar fecal testing for colon cancer annually and at any age)
   i. This multitargeted stool DNA test with fecal immunochemical testing is currently a standard test and a yearly interval is in line with validated screening recommendations.
   ii. Guidelines including USPTF suggest an interval of every 1-3 years is reasonable within certain age ranges. The recommended age range used to be 50-75 but now includes 45-50 given changing patterns in cancer incidence. **Of note, nowhere is it recommended that the use of these tests can start "at any age."**
   iii. Cologuard is **NOT** indicated for routine screening of patients at "high risk" – only for high risk patients that are unwilling or unable to undergo colonoscopy.

D. Colonoscopy – Colonoscopy is the gold standard and is currently recommended every 10 years for standard risk patient and every 5 years for screening in moderately high risk patients. Dr. Kaplan recommends considering this population of patients that took VCDs high risk and decreasing the recommended screening interval to every 5 years.
   i. The benefit of colonoscopy includes the early detection of a colorectal cancer at a curable stage. Additionally, the removal of polyps may prevent progression to malignancy since colorectal carcinogenesis is well described with a pattern of development over years and even decades. Again there is no known increased risk of developing colorectal cancer with nitrosamines to justify more frequent colonoscopies.
   ii. There are also major risks of this invasive procedure including sedation, cardiopulmonary complications, reactions to bowel preparation (fluid and electrolyte imbalance), nausea, vomiting, aspiration, falls, bleeding, infection, and perforation. Perforation is the most serious common complication of colonoscopy happening in 0.016% to 0.8% and can be operator/condition dependent. There is also a complication known at traumatic perforation. If perforation is identified during or after procedure, immediate abdominal imaging and surgical evaluation is required.
   iii. Aggressive bowel preparation is required for adequate visualization and there can be issues with the different available preparations. Elderly patients are known to suffer increased risk of aspiration, vomiting and falls from dehydration. Admission to hospital for bowel preparation is rare today though it used to be the standard procedure.[46] Poor bowel preparation necessitates repeating the colonoscopy, including repeat of bowel preparation.
   iv. Older age, comorbidity and the use of anticoagulant therapy increase risk of harm during colonoscopy.[47]

[46] Church, J. Complications of Colonoscopy. Gastroenterology Clin N Am 42 (2013) 639-657.
[47] Rosen L, Bub DS, Reed JF 3rd, Nastasee SA. Hemorrhage following colonoscopic Polypectomy Dis Colon Rectum. 1993 Dec; 36(12):1126-31.

v. In screening populations, an overall post-colonoscopy complication rate of 2.8/1000 procedures reported.
vi. Inherited susceptibility is the most identifiable risk that decreases recommended colonoscopy interval from standard 10 to 5 or fewer years. Others include polyposis syndromes, inflammatory bowel disease, and patients that have had abdominal radiation.
vii. There are **NO** identified clinical or environmental risk factors/exposures that change the current guidelines of every 10 years including but not limited to consumption of red meat or processed meat or grilled/barbequed meat.

E. Upper Endoscopy – Dr. Kaplan recommends upper endoscopy every 5 years or more based on symptoms as well as smoking and alcohol history, but he fails to elaborate on how smoking and/or alcohol history would impact his interval recommendation as implied.
i. I view this as the most astonishing and riskiest recommendation of Dr. Kaplan's entire list.
ii. There are no formal recommendations for upper endoscopy in the USPSTF screening guidelines. There is no formal cancer screening recommendation for upper endoscopy every 5 years for any cancer.
iii. Barrett's Esophagus is known to increase the risk of developing esophageal adenocarcinoma – annual cancer incidence with BE is between 1-3%. However, screening for Barrett's Esophagus, even in high risk patients (GERD, age, male, central obesity) is not formally recommended by the USPSTF.
iv. Surveillance endoscopy for <u>known</u> potentially precancerous Barrett's Esophagus is controversial and the evidence of benefit is mixed. The current guideline from the American Society of Gastrointestinal Endoscopy is that it is reasonable to do endoscopy <u>once</u> but that there is still no clear survival benefit shown in this known high risk population. There certainly is no suggestion of an upper endoscopy every 5 years or more frequently and alcohol and tobacco history do no impact any of the guidelines for surveillance of esophageal cancer.
v. The risks associated with esophagogastroduodenoscopy include sedation, hypoxemia, hypoventilation, airway obstruction, dental breakage, aspiration, and infection.

F. Low dose CT Chest Scan – especially in smokers or prior smokers.
i. Tobacco smokers were studied in U.S. National Lung Screening Trial (NLST), which was a randomized clinical trial of annual screening. The high risk patients were determined to be adults 55-74 years of age with at least a 20 pack year history. It is notable that the criteria for high risk are based entirely on age and smoking history[48] and not any other potential exposure or carcinogen.
ii. NLST showed reduced risk in the population of current smokers and those that discontinued within 15 years of enrollment.
iii. The number needed to screen to prevent 1 death was 320 patients.
iv. Even exposure to the known carcinogen asbestos does not mandate a recommendation for yearly LDCT. Asbestos-exposed individuals are estimated to have two-fold or more risk of lung cancer at baseline but are

[48] Fitzgerald, NR. Eligibility for low-dose computerized tomography screening among asbestos-exposed individuals. Scand J Work Environ Health. 2015 Jul; 41(4):407-12.

only eligible for LDCT if they meet the required duration of pack year history and age criteria.

v. It is hard to equilibrate the level of risk of LDCT (radiation, risk of false positive and invasive biopsy) conferred by significant tobacco risk with the indeterminate and unverified contribution of nitrosamines to human lung cancer risk.

vi. Low dose CT chest scan does have significantly less radiation than standard CT chest but annual exposure to radiation for an indeterminate risk and undefined benefit is unnecessary and risky.

Response to Conclusion Statements by Dr. Kaplan regarding Patients Exposed to VCDs with potential NDMA/NDEA Contaminants.

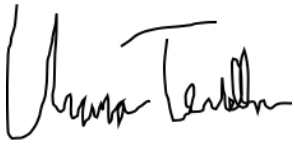
Dr. Kaplan "believes to a reasonable degree of medical certainty that there exist diagnostic tests that can mitigate the risks of developing cancer." Contrary to Dr. Kaplan's belief, screening tests are designed to detect cancers earlier and at treatable stages but will not mitigate the risk of developing any of these cancers. No screening test can PREVENT development of any cancer and that is not the goal of screening protocols. Additionally, it is not clear that any of these patients are at *any* increased risk of developing cancers or that their cancers would progress/spread at a different pace than any others. Given the absolute lack of data of additional risk of developing any of these cancers in humans based on this level of exposure or any level of exposure, the "enhanced medical monitoring" recommended by Dr. Kaplan confers real risk to VCD treated patients without any appreciable clinical benefit. I appreciate that Dr. Kaplan is well meaning and trying to help their general health status but I sincerely worry that this enhanced monitoring schema is misguided and harmful.

It is not clear from any of the data I have reviewed on valsartan that nitrosamine exposure increases the pre-test probability of developing any cancer in the human patients and therefore merits changes in validated screening tests and intervals. And perhaps most notably, our standardized cancer screening timelines for asymptomatic patients are not adjusted on the basis of any exposure, even those exposures firmly established to contribute to development of cancer. The only modifications are based on known hereditary cancer syndromes, illnesses known to increase risk of cancer, and prior personal history of malignancy. The only exposure that justifies any special testing is tobacco usage and use of LDCT and the associated risk/benefit ratio is tightly defined by pack year history in a specific age range.

FIRST DO NO HARM – Primum Non Nocere – is attributed to the ancient Greek physician Hippocrates and remains one of the founding principles of modern medicine today. This statement in some form is part of the pledge/oath we take upon graduation from medical school. Do No Harm is actually a strong motivator of the principle of guideline-driven cancer screening given the real risks involved with screening tests. I am deeply concerned that Dr. Kaplan's recommendations for enhanced screening are without scientific merit and have real potential to harm the very patient population he is hoping to help. My life's passion is fighting cancer – I despise cancer – I would be delighted to have a world without cancer with a close second being catching every cancer early at a curable stage. That said, I am equally concerned about harming patients with unnecessary or risky interventions – and older patients are the most vulnerable to complications from procedures. These older patients are more likely to develop cancer based on age as a primary risk factor as well as the most likely to have been/be treated for hypertension, acute coronary syndrome, heart failure, and renal disease. I am very fearful for any patients subjected to Dr. Kaplan's proposed monitoring protocol because it is without scientific underpinning, is not consensus approved, and carries real potential for harm

in these unselected patients without verifiable risk factors. Dr. Kaplan's proposed monitoring protocol does not meet the standard of "FIRST DO NO HARM" essential to our principles of the safe and informed practice of medicine.

Sincerely,



Ursina R. Teitelbaum, MD

TEITELBAUM

EXHIBIT A

List of Materials Reviewed in Preparation of this Document

- 11/1/2021 Consolidated Third Amended Medical Monitoring Class Action Complaint
- Report and CV of Mahyar Etminan, Pharm.D., MSc.D.
- Report and CV of Stephen S. Hecht, Ph.D.
- Report and CV of Dipak Panigraphy, M.D.
- Report and CV of David Madigan, Ph.D.
- Report and CV of Stephen M. Lagana, MD
- Report and CV of Daniel Catenacci, M.D.
- Report and CV of Michael Bottorff, Pharm.D.
- Report and CV of Janice K. Britt, Ph.D.
- Report and CV of Lewis A. Chodosh, M.D., Ph.D.
- Report and CV of John Flack, M.D., M.P.H.
- Report and CV of Jon P. Fryzek, M.P.H., Ph.D.
- Report and CV of Herman J. Gibb, Ph.D., M.P.H.
- Report and CV of Dr. George Johnson
- Report and CV of Lee-Jen Wei, Ph.d.

TEITELBAUM EXHIBIT B

Ursina R. Teitelbaum, M.D.
Curriculum Vitae

Demographic and Personal Information

Current Appointment

2018-present Deenie Greitzer and Daniel G. Haller Gastrointestinal Medical Oncology Professorship
Perelman School of Medicine, University of Pennsylvania
2015-present Associate Professor of Clinical Medicine
Perelman School of Medicine, University of Pennsylvania

Personal Data

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Education/Training

Undergraduate

1987-1991	Bachelor of Arts, History, German Literature, Duke University, Durham, NC
1993-1994	Postbaccalaureate Premedical Program, Goucher College, Towson, MD

Doctoral/Graduate

1995-1999	Medical Doctorate (M.D.), University of Maryland School of Medicine; MD

Postdoctoral/Graduate

1994	Merck Summer Research Fellowship; Laboratory of Stephen Everett; MD
1999-2000	Intern, Internal Medicine, University of Chicago, Chicago, IL
2000-2002	Resident, Internal Medicine, University of Chicago, Chicago, IL
2002-2005	Fellow, Medical Oncology, University of Chicago, Chicago, IL
2002-2005	Fellow, Geriatric Medicine, University of Chicago, Chicago, IL
2004-2005	Clinical Research Training Program (certificate) University of Chicago, IL
2015	Cooper Leadership Training Program, The Wharton School, PA

Faculty/Professional Appointments

1991-1993	Equity Sales, Deutsche Bank Capital Corporation, New York, NY
2005-2006	Clinical Associate, Hematology/Oncology Division, University of Chicago, IL
2005-2006	Clinical Associate, Section of Geriatrics, University of Chicago, IL
2007-2015	Assistant Professor of Clinical Medicine, University of Pennsylvania, Perelman School of Medicine, Philadelphia, PA
2015-present	Associate Professor of Clinical Medicine, University of Pennsylvania, Perelman School of Medicine, Philadelphia, PA

Hospital/Administrative Appointments

2009-2015	Clerkship Director, Hematology/Oncology Outpatient Elective, University of Pennsylvania, Perelman School of Medicine, Philadelphia, PA
2010-present	Core Faculty, Hematology/Oncology, Internal Medicine Residency, Hospital of the University of Pennsylvania, Philadelphia, PA
2012-present	Leader, Pancreas Service Line, Abramson Cancer Center, Philadelphia, PA
2012-2015	Reviewer, Pancreatic Cancer. ECRI-Penn AHRQ Evidence-Based Practice Center, University of Pennsylvania, Philadelphia, PA
2015-present	Physician Leader, Survivorship Program, University of Pennsylvania
2015-present	Clinical Director, Penn Pancreatic Cancer Research Center, University of Pennsylvania, Philadelphia, PA
2016-present	GI Cancer Pathway Development Oncology Lead, Abramson Cancer Center
2017-present	EPIC Lead, Hematology/Oncology Division, Department of Medicine, University of Pennsylvania
2017-present	EPIC Governance, Department of Medicine, University of Pennsylvania
2017-present	Physician Lead, Gastrointestinal Cancer Survivorship Clinic

Licensure and Board Certification

2005-present	ACLS/BLS Certification
2005-present	Federal Drug Enforcement Administration Registration
2006-present	Pennsylvania, #MD430295
2020-present	New Jersey
2002	Internal Medicine, American Board of Internal Medicine (ABIM), certified
2005	Geriatric Medicine, ABIM, Certificate of Added Qualifications
2006	Medical Oncology, ABIM, certified
2012	Hospice and Palliative Medicine, ABIM, certified
2016	Medical Oncology, ABIM, recertified

Honors, Awards, and Accomplishments

1990	Delta Phi Alpha German Honor Society, Duke University
1989-1991	Dean's List with Distinction, Duke University
1995-1999	Summa Cum Laude; Class Rank 1 of 110, University of Maryland School of Medicine, Baltimore, MD
1998	Alpha Omega Alpha Honor Medical Society Inductee, Junior Year
1999	Faculty Gold Medal for Valedictorian, University of Maryland School of Medicine
1999	Theodore Woodward Prize in Internal Medicine for Excellent Qualifications in the Field of Internal Medicine, University of Maryland School of Medicine
1999	NIH Grant for Clinical Rotation in Tropical Medicine, Bamako, Mali
2002-2005	ASCO Geriatrics/Oncology Training Program Development Grant, Hartford Foundation
2013	Humanism and Professional Award, Department of Medicine, University of Pennsylvania, Perelman School of Medicine
2013	Carole P. and F. Otto Haas Junior Faculty Award
2014	Academy of Master Clinicians, University of Pennsylvania
2015	Chair, Purple Stride 2015, Pancreatic Cancer Action Network, Philadelphia
2015	Deenie Greitzer and Daniel G Haller Gastrointestinal Medical Oncology

Professorship, University of Pennsylvania

Professional Organizations and Societies

1998	Alpha Omega Alpha Medical Honor Society (member)
2002-present	American Geriatrics Society (member)
2004-present	American Society of Clinical Oncology (member)

Teaching Experience/Responsibilities

1996	Biochemistry Instructor, Prematriculation Summer Program, University of Maryland School of Medicine
1996-1999	Peer Tutor, University of Maryland School of Medicine
1999-2002	Resident Preceptor, History Taking and Physical Diagnosis, Pritzker School of Medicine, University of Chicago
2004-2006	Laboratory Instructor, Hematologic Disease Module; Clinical Pathophysiology and Therapeutics, Pritzker School of Medicine, University of Chicago
2005-2006	Coordinator, Fellows Board Review Course, University of Chicago
2014-present	Director, GI Multidisciplinary Tumor Board, CME Certified
2015-present	Co-Lead, Hematology/Oncology Fellowship Tumor Board

Publications

Manuscripts

1. **Teitelbaum UR**, Haller DG. Second-line XELOX or FOLFOX-4 for metastatic colorectal cancer. *Nature Reviews Clinical Oncology*. 2009 May;6(5):250-1.
2. Wade AN, Cheng G, **Teitelbaum UR**, Patel AA, Alavi A, Rickels MR. Amelioration of hypoglycemia with octreotide therapy in metastatic octreotide therapy in metastatic insulinoma with positive octreotide scan. *Pancreas*. 2011 Jan;40(1):173-5.
3. Sun W, Sohal D, Hallder DG, Mykulowycz K, Rosen M, Soulen MC, Caparro M, **Teitelbaum UR**, Giantonio B, O'Dwyer PJ, Shaked A, Reddy R, Olthoff K. Phase 2 trial of bevacizumab, capecitabine, and oxaliplatin in treatment of advanced hepatocellular carcinoma. *Cancer*. 2011 Jul 15;117(14):3187-92.
4. Beatty GL, Chiorean EG, Fishman MP, Saboury B, **Teitelbaum UR**, Sun W, Huhn RD, Song W, Li D, Sharp LL, Torigian DA, O'Dwyer PJ, Vonderheide RH.CD40 agonists alter tumor stroma and show efficacy against pancreatic carcinoma in mice and humans. *Science*. 2011 Mar 25;331(6024):1612-6.
5. Sohal DP, Metz JM, Sun W, Giantonio BJ, Plastaras JP, Ginsberg G, Kochman ML, **Teitelbaum UR**, Harlacker K, Heitjan DF, Feldman MD, Drebin JA, O'Dwyer PJ. Toxicity study of gemcitabine, oxaliplatin, and bevacizumab, followed by 5-fluorouracil, oxaliplatin, bevacizumab, and radiotherapy, in patients with locally advanced pancreatic cancer. *Cancer Chemotherapy and Pharmacology*. 2013 Jun;71(6): 1485-91.
6. Jones JA, Patel VB, Goldsmith B, **Teitelbaum UR**, Plastaras JP. Diffusely metastatic digital papillary adenocarcinoma 11 years after initial presentation treated with palliative chemotherapy and radiotherapy. *Journal of Clinical Oncology*. 2013 Aug; 31(22): e386-9.
7. Beatty GL, Torigian DA, Chiorean EG, Saboury B, Brothers A, Alavi A, Troxel AB, Sun W, **Teitelbaum UR**, Vonderheide RH, O'Dwyer PJ. A phase I study of an agonist CD40 monoclonal antibody (CP-870,893) in combination with gemcitabine in patients with advanced pancreatic ductal adenocarcinoma. *Clinical Cancer Research*. 2013 Nov 15;19(22): 6286-95.

8. Sohal DP, Mykulowycz K, Uehara T, **Teitelbaum UR**, Damjanov N, Giantonio BJ, Carberry M, Wissel P, Jacobs-Small M, O'Dwyer PJ, Sepulveda A, Sun W. A phase II trial of gemcitabine, irinotecan and panitumumab in advanced cholangiocarcinoma. *Annals of Oncology*. 2013 Dec;24(12): 3061-5.
9. Treadwell J, Mitchell M, Eatmon K, Jue J, Zafar H, **Teitelbaum UR**, Schoelles K. Imaging tests for the diagnosis and staging of pancreatic adenocarcinoma. *Agency for Healthcare Research and Quality* 2014.
10. Grover S, Jones JA, **Teitelbaum UR**, Apisarnthanarax S. Radiation recall myositis: two sites, one patient. *Practical Radiation Oncology*.2015 Jan-Feb;5(1): 39-42.
11. Datta J, McMillan MT, Shang EK, Mamtani R, Lewis RS Jr, Kelz RR, **Teitelbaum UR**, Plastaras JP, Drebin JA, Fraker DL, Karakousis GC, Roses RE. Omission of adjuvant therapy after gastric cancer resection: development of a validated risk model. *Journal of the National Comprehensive Cancer Network*.2015 May;13(5): 531-41.
12. Riff BP, Yang YX, Soulen MC, Pryma DA, Bennett B, Wild D, Nicolas G, **Teitelbaum UR**, Metz DC. Peptide receptor radionuclide therapy-induced hepatotoxicity in patients with metastatic neuroendocrine tumors. *Clinical Nuclear Medicine*. 2015 Nov;40(11): 845-50.
13. McMillan MT, Lewis RS, Drebin JA, **Teitelbaum UR**, Lee MK, Roses RE, Fraker DL, Vollmer CM. The efficacy of adjuvant therapy for pancreatic invasive intraductal papillary mucinous neoplasm (IPMN). *Cancer*. 2016 Feb 15;122(4): 521-33.
14. Treadwell JR, Zafar HM, Mitchell MD, Tipton K, **Teitelbaum UR**, Jue J. Imaging tests for the diagnosis and staging of pancreatic adenocarcinoma: a meta-analysis. *Pancreas*. 2016 Jul;45(6): 789-95.
15. Levy JL, Sudheendra D, Dagli M, Mondschein JI, Stavropolous SW, Shlansky-Goldberg RD, Tretola SO, **Teitelbaum UR**, Soulen MD. Percutaneous biliary drainage effectively lowers serum bilirubin to permit chemotherapy treatment. *Abdominal Radiology* (NY), 2016 Feb;41(2): 317-23.
16. Boimel PJ, Berman AT, Li J, Apisarnthanarax S, Both S, Lelionis K, Larson GL, **Teitelbaum UR**, Lukens JN, Ben-Josef E, Metz JM, Plastaras JP. Proton beam reirradiation for locally recurrent pancreatic adenocarcinoma. *Journal of Gastrointestinal Oncology*. 2017 Aug;8(4): 665-674.
17. Katona BW, Roccaro GA, Soulen MC, Yang YX, Bennett BJ, Riff BP, Glynn RA, Wild D, Nicolas GP, Pryma DA, **Teitelbaum UR**, Metz DC. Efficacy of peptide receptor radionuclide therapy in a United States based cohort of metastatic neuroendocrine tumor patients: Single-institution retrospective analaysis. *Pancreas*. 2017 Oct;46(9): 1121-1126.
18. Clasen SC, Ky B, O'Quinn R, Giantonio B, **Teitelbaum UR**, Carver JR. Fluoropyrimidine-induced cardiac toxicity: challenging the current paradigm. *Journal of Gastrointestinal Oncology*. 2017 Dec;8(6): 970-979.
19. Shabason JE, Chen J, Apisarnthanarax S, Damjanov N, Giantonio B, Loaiza-Bonilla A, O'Dwyer PJ, O'Hara, M, Reiss KA, **Teitelbaum UR**, Wissel P, Drebin JA, Vollmer C, Kochman M, Mick R, Vergara N, Jhala N, Doucette A, Lukens JN, Plastaras JP, Metz JM, Ben-Josef E. A phase I dose escalation trial of nab-paclitaxel and fixed dose radiation in patients with unresectable or borderline resectable pancreatic cancer. *Cancer Chemotherapy Pharmacology*. 2018 Mar;81(3): 609-614.
20. Lubner S, Feng Y, Mulcahy M, O'Dwyer P, Giang GY, Hinshaw JL, Deming D, Klein L, **Teitelbaum UR**, Payne J, Engstrom P, Stella P, Meropol N, Benson A. E4206: AMG 706 and octreotide in patients with low-grade neuroendocrine tumors. *Oncologist*. 2018 Sep:23(9): 1006-e104.
21. Soulen MC, van Houten D, **Teitelbaum UR**, Damjanov N, Cengel KA, Metz DC. Safety and feasibility of integrating Yttrium-90 radioembolization with capecitabine –temozolomide for grade 2 liver-dominant metastatic neuroendocrine tumors. *Pancreas*. 2018 Sep;47(8): 980-984.
22. Bauman B, Mick R, Martinez E, Lawless TM, Zinck L, Sinclair P, Fuhrer M, O'Hara M, Schneider CJ, O'Dwyer P, Plastaras J, **Teitelbaum UR**, Reiss KA. Efficacy of oral cryotherapy during oxaliplatin infusion in preventing oral thermal hyperalgesia: a randomized trial. *Journal of National Comprehensive Cancer Network*. 2019 Apr;17(4): 358-364.
23. Karasic TB, O'Hara MH, Loaiza-Bonilla A, Reiss KA, **Teitelbaum UR**, Borazanci E, De Jesus-Acosta A, Redlinger C, Burrell JA, Laheru DA, Von Hoff DD, Amaravadi RK, Drebin JA, O'Dwyer PJ. Effect of gemcitabine and nab-paclitaxel with or without hydroxychloroquine on patients with advanced

pancreatic cancer: a phase 2 randomized clinical trial. *Journal of the American Medical Association Oncology*. 2019 July;5(7): 993-998.

24. Karasic TB, O'Hara MH, **Teitelbaum UR**, Damjanov N, Giantonio BJ, d'Entrement TS, Gallagher M, Zhang PJ, O'Dwyer PJ. Phase II trial of palbociclib in patients with advanced esopheal or gastric cancer. *Oncologist*. 2020 Dec;25(12) e1864-e1868.
25. Varughese LA, Lau-Min KS, Cambareri C, Damjanov N, Massa R, Reddy N, Oyer R, **Teitelbaum UR**, Tuteja S. DPYD and UGT1A1 Pharmacogenetic testing in patients with gastrointestinal malignancies: an overview of the evidence and considerations for clinical implementation. *Pharmacotherapy*. 2020 Nov;40(11): 1108-1129.
26. Reiss KA, Mick R, O'Hara MH, **Teitelbaum UR**, Karasic TB, Schneider CJ, Cowden S, Southwell T, Romeo J, Izgur N, Hannan ZM, Tondon R, Nathanson K, Vonderheide RH, Wattenberg MM, Beatty G, Domchek SM. Phase II study of maintenance rucaparib in patients with platinum-sensitive advanced pancreatic cancer and a pathogenic germline or somatic variant in BRCA1, BRCA2, or PALB2. *Journal of Clinical Oncology*. 2021 Aug 1;39(22): 2497-2505.
27. Perkons NR, Kim C, Boedec C, Keele LJ, Schneider C, **Teitelbaum UR**, Ben-Josef E, Gabriel PE, Plastaras JP, Shulman LN, Wojcieszynski AP. Quantifying the impact of the COVID-19 pandemic on gastrointestinal cancer care delivery. *Cancer Reports*. 2021 June 17: e1427.
28. Arscott WT, Nead KT, Bear A, Venigalla S, Shabason J, Lukens JN, Plastaras JP, Wojcieszynski A, Metz J, O'Hara M, Reiss KA, **Teitelbaum UR**, Loaiza-Bonilla A, Drebin J, Lee MK, Schroff SG, Ben-Josef E. Concurrent nab-paclitaxel and radiotherapy: novel radiosensitization for borderline resectable or unresectable pancreatic cancer. *American Journal of Clinical Oncology*. 2021 Sept 1;44(9): 469-474.
29. Lau-Min KS, Varughese LA, Nelson MN, Cambareri C, Reddy NJ, Oyer RA, ***Teitelbaum UR***, Tuteja S. Preemptive pharmacogenetic testing to guide chemotherapy dosing in patients with gastrointestinal malignancies: a qualitative study of barriers to implementation. *BMC Cancer*. 2022 Jan 8;22(1):47.

Chapter

Teitelbaum Ursina. Chapter 21: Important of Supportive and Palliative Care in Gastrointestinal Malignacies. Multidisciplinary Management of Gastrointestinal Cancers. Edited by Weijing Sun. World Scientific, 2017:555-597.

Conferences/Presentations

1. Geriatric Oncology Case Presentations: Clinical Issues in the Management of the Older Patient with Cancer (CME) 2002, Chicago, IL
2. Gastrointestinal Cancer in the Older Patient: University of Chicago's Third Annual Geriatric Oncology Conference (CME) 2003, Chicago, IL
3. TPMT Deficiency: A Case Study in Pharmacogenetics: University of Chicago Hematology/Oncology Grand Rounds 2003, Chicago, IL
4. When Back Pain is not Benign: Review of the Applications of Vertebraplasty: University of Chicago Hematology/Oncology Grand Rounds 2004, Chicago, IL
5. Pain Management in the Elderly Cancer Patient: University of Chicago Hematology/Oncology Grand Rounds 2004, Chicago, IL
6. Gastrointestinal Malignancy: Review of Therapeutic Modalities. Clinical Nutrition Conference (CME) 2005, Chicago, IL
7. Overview of Esophageal and Gastric Cancer: Focus on Gastrointestinal Cancers. Perelman School of Medicine, University of Pennsylvania, 2007-present (yearly)
8. Updates in Oncologic Management of Hepatocellular Carcinoma: Society of Interventional Radiology National Meeting.2008, Washington, D.C.

9. Medical Management and the Effect of Biology on Therapy for Hepatic Colorectal Cancer Metastases: Radiologic Society of North America 2009, Chicago, IL
10. Systemic Therapies for Colon Cancer Metastases: How Far Can They Take Us: World Conference on Interventional Oncology, 2011, Philadelphia, PA
11. Pancreas Cancer in 2013: State of the Art: Gastroenterology Grand Rounds – David Ginsberg Memorial Invited Speaker 2013, Philadelphia, PA
12. Medical Therapy for Neuroendocrine Tumors: Octreotide, Chemotherapy, and Targeted Therapy: Updates in Neuroendocrine Tumors Annual Conference, 2014-present, Philadelphia, PA
13. Penn Updates from International Meetings: Gastrointestinal Oncology (CME) 2014-yearly, Philadelphia, PA
14. Progress in Pancreatic Cancer Therapy: Third Annual David K. Ginsberg MD Lectureship.2015: Philadelphia, PA
15. Director, GI Multidisciplinary Tumor Board,(CME) Weekly: 2014-present, Philadelphia, PA
16. Co-Lead Hematology/Oncology Fellowship Tumor Board – Weekly, 2018-present.

TEITELBAUM
EXHIBIT C

Below is my fee schedule:

Record Review **Research** **Preparation of Reports** **Attorney Meetings** **Teleconferences**	**$850/hour**
Travel Time	**$500/hour**
Deposition- ***Payment Required in Advance*** (Two Hour Retainer Required) **Additional time billed at:**	**$1,500/hour** **$1,500/hour**
Live Testimony – ***Payment Required in Advance***	
Full Day	**$10,000**
Half Day	**$ 6,500**